Docket No.: PF-0195-2 RCE

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1642

Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal Brief-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 on March 10, 2004.

By: Shirley A. Recipon Printed: ~~Katherine Stofer~~ Shirley A. Recipon

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Hillman et al.

Title:	A NOVEL PROSTATE-ASSOCIATED KALLIKREIN		
Serial No.:	09/170,980	Filing Date:	October 13, 1998
Examiner:	Davis, Minh-Tam	Group Art Unit:	1642

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed December 8, 2003, and received by the USPTO on December 10, 2003, herewith are three copies of Appellants' Brief on Appeal. **Please note that the period for response has been extended until March 10, 2004 by the accompanying Petition and fee.** Authorized fees include **$110.00** for a one-month extension of time and the $ **330.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 1 and 18-20 of the above-identified application.

03/17/2004 AWONDAF1 00000102 090108 09170980
01 FC:1402 330.00 DA

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to **Incyte Pharmaceuticals, Inc. (now Incyte Corporation, formerly known as Incyte Genomics, Inc.)** (Reel 8611, Frame 0650), which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants assignee, **Incyte Pharmaceuticals, Inc. (now Incyte Corporation, formerly known as Incyte Genomics, Inc.)** (Reel 9634, Frame 0127), is also the real party in interest in related Appeal No. 2003-1604, filed August 20, 2001, and received by the USPTO on August 23, 2001, in the application assigned United States Serial Number 09/532,270, filed March 21, 2000. It is Appellants understanding that a decision in Appeal No. 2003-1604 will have a direct effect or be directly affected by or bearing on the Board's decision in the pending appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 1 and 18-20
Claims allowed:	(none)
Claims canceled:	Claims 2-17, 21-26
Claims withdrawn:	27-32
Claims on Appeal:	Claims 1 and 18-20 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed *inter alia*, to a novel human prostate-associated kallikrein protein, abbreviated as HPAK, and naturally-occurring amino acid sequences at least 90% identical to the amino acid sequence of SEQ ID NO:1 over the entire length of SEQ ID NO:1. HPAK is a

polypeptide sequence encoded by a gene that is expressed in humans. The novel polypeptide is demonstrated in the specification and in subsequent analyses *infra* to be a member of the serine protease family and kallikrein subfamily (Specification, p. 1, lines 7-8; p. 11, lines 6-12). As such, the claimed invention has numerous practical, beneficial uses in the diagnosis of acquired and inherited disease, expression profiling, and drug development, none of which require knowledge of how the polypeptide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

HPAK shares chemical and structural homology with human pancreatic kallikrein (GI 186653). In particular, HPAK shares 54% identity with GI 186653, including the conserved amino acid residues for serine protease activity, H_{65} D_{113}, and S_{206}. Also conserved are 10 cysteine residues (31, 50, 66, 145, 166, 177, 191, 202. 212, and 227; see Figure 2) which are structurally important and involved in the formation of five disulfide bonds, as well as D_{200}, which likely confers chymotrypsinogen-like activity on HPAK. The similar hydrophobicity plots of HPAK and GI 186653 (Figures 3 and 4) indicate that these molecules have a similar structure (Specification, p. 11, lines 6-17).

The similarity of the claimed polypeptide to another polypeptide of known, undisputed utility by itself demonstrates utility beyond the reasonable probability required by law. HPAK is, in that regard, homologous to human pancreatic kallikrein.

(6) ISSUES

1. Whether claims 1 and 18-20 directed to novel human kallikrein polypeptide sequences meet the utility requirement of 35 U.S.C. §101.

2. Whether the known properties of kallikrein 11, a polypeptide that is encompassed by the claimed 90% variants of SEQ ID NO:1, are sufficient to enable utiltiy for the claimed polypeptides.

3. Whether claims 1 and 18-20 meet the enablement requirement of 35 U.S.C. § 112, first paragraph, i.e., would the specification enable one of ordinary skill in the art to make and use the claimed polynucleotides, e.g., for toxicology testing, drug development, and the diagnosis of disease.

4. Whether claims 1 and 18-20 and the specification provides an enabling disclosure commensurate in scope with the claims so as to satisfy the enablement requirement of 35 U.S.C. §112,

first paragraph.

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

All of the claims on appeal are grouped together.

As to Issue 4

All of the claims on appeal are grouped together.

(8) APPELLANTS' ARGUMENTS

Appellants note that claim 26 was canceled in the Office Action Response mailed July 3, 2003. However, the Examiner states that claims 1, 18-20 and 26 are rejected (Office Action, September 8, 2003; page 1; Paper No. 37). Appellants' arguments will therefore hereinafter reflect the fact that claim 26 was canceled.

ISSUES 1 and 2: **The rejection of claims 1 and 18-20 is Improper, as the Inventions of Those Claims Have a Patentable Utility as Set Forth in the Instant Specification, and/or a Utility Well Known to One of Ordinary Skill in the Art.**

Claims 1 and 18-20 stand rejected under 35 U.S.C. § 101, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that:

- there is no indication that SEQ ID NO:1 has serine protease activity (Paper No. 37, Final Office Action, September 8, 2003, page 3).
- the claimed 90% variants encompass kallikrein 11, however, Applicant has not disclosed how to make the claimed variants that have serine protease activity. That is, in the specification and

> the claims it has not been shown which sequence of SEQ ID NO:1 confers serine protease, such that one can make a variant of SEQ ID NO:1 that has serine protease activity. (Paper No. 37, Final Office Action, September 8, 2003, page 3) (emphasis in original).

The invention at issue, identified in the patent application as a novel human prostate-associated kallikrein, abbreviated as HPAK, is a polypeptide sequence encoded by a gene that is expressed in breast and prostate tissues of humans (Figure 5; specification, p. 11, lines17-19). The novel polypeptide is demonstrated in the specification to be a member of the class of serine proteases, whose biological functions include prostate specific antigen (PSA), a human serine protease that is a well-known marker for prostatic cancer as well as for other disorders of the prostate (specification at pp. 1-2). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions. In particular, HPAK levels can be used as a basis to diagnose altered or abnormal levels of HPAK and as a disease marker for monitoring cancer progression, response to therapy and to differentiate patients with benign prostate hyperplasia from those with adenocarcinoma of the prostate (specification, pages 1-2; page 10, lines 26-28; page 23, lines 16-22; page 32, lines 15-19 and lines 24-28).

The similarity of the claimed polypeptide to another polypeptide of known, undisputed utility by itself demonstrates utility beyond the reasonable probability required by law. HPAK is, in that regard, homologous to GI 186653, a human pancreatic kallikrein (KLK1), which shares about 54% sequence identity with HPAK (specification, page 11). In particular, HPAK contains a signal sequence important for kallikrein secretion (Figures 2, 3, and 4), residues H_{65}, D_{113}, and S_{206}, critical for serine protease activity, residue D_{200} which is likely to confer on HPAK chymotrypsinogen-like activity, 10 conserved cysteine residues (31, 50, 66, 145, 166, 177, 191, 202, 212, and 227; Fig. 2) which are structurally important and form five disulfide bonds and as illustrated by Figures 3 and 4, HPAK and human pancreatic kallikrein have rather similar hydrophobicity plots (specification, page 11, lines 8-17).

This is more than enough homology to demonstrate a reasonable probability that the utility of human pancreatic kallikrein can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino

acid residues is exceedingly small (Brenner et al., Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998), of record). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to human pancreatic kallikrein is, accordingly, very high.

There is, in addition, direct proof of the utility of the claimed invention. Appellants have submitted the Declaration of Furness (of record, submitted August 1, 2002) describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ 11).

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the claimed polypeptide does not have serine protease activity. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to

possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Homology of the Claimed Polypeptide to Another Polypeptide Having a Known Function/Activity Demonstrates Utility Beyond the Reasonable Probability Required by Law

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's Specification. Additionally, these uses are explained, in detail, in the Furness Declaration, **discussed *infra*.** Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The similarity of the claimed polypeptide to another of undisputed utility demonstrates utility

Because there is a substantial likelihood that the claimed HPAK polypeptide is functionally related to human pancreatic kallikrein and human kallikrein 11 (see Exhibit A, mailed 10/17/02; alignment faxed 1/28/03), polypeptides of undisputed utility, there is by implication a substantial likelihood that the claimed HPAK polypeptide is similarly useful. Appellants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed, and readily apparent from the patent application, that the claimed HPAK

polypeptide shares 54% sequence identity with human pancreatic kallikrein. This is more than enough homology to demonstrate a reasonable probability that the utility of human pancreatic kallikrein can be imputed to the claimed HPAK polypeptide. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. (Brenner et. al., *supra.*) Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed HPAK polypeptide is related to human pancreatic kallikrein is, accordingly, very high.

The Examiner must accept Appellants' demonstration that the homology between the claimed HPAK polypeptide and pancreatic kallikrein (GI 186653) and kallikrein 11 demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

While the Examiner has cited literature (Bowie et al., Lazar et al., and Burgess et al.) identifying some of the difficulties that may be involved in predicting protein function, none suggest that functional homology cannot be inferred by a reasonable probability in this case. Importantly, none contradict Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. At most, these articles individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

B. SEQ ID NO:1 Is an Expressed Protein

There is a substantial likelihood that SEQ ID NO:1 is an expressed protein. Appellants are not aware of reports of post-translation regulation of expression for the kallikrein gene family.

Moreover, the Examiner has again relied on the novel theory that the central dogma of molecular biology (*i.e.*, DNA directs transcription of messenger RNA which in turn directs translation of

protein) somehow does not apply to the discoveries of the present application. That is, the nucleotide sequence of SEQ ID NO:2 (which encodes the polypeptide of SEQ ID NO:1) was determined from a human cDNA library. That cDNA library in turn was made from messenger RNA isolated from human tissue. See the specification, for example, at pages 37-38. Thus, the nucleotide sequences of the present invention are expressed sequences. The Examiner asserts that the existence of an expressed mRNA does not insure that the protein encoded by the mRNA will be translated and, hence, the claimed subject matter lacks patentable utility.

Regulation of gene expression occurs at many levels, including transcription, splicing, polyadenylation, mRNA stability, mRNA transport and compartmentalization, translation efficiency, protein modification, and protein turnover. While steady state mRNA levels are not always directly proportional to the amount of protein produced in a cell, mRNA levels are **routinely** used as an indicator of protein expression. Countless scientific publications have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Moreover, mRNA levels are **usually** a good indicator of protein levels in a cell. According to B. Lewin [(1997) Genes VI Oxford University Press, Inc. New York, NY] (of record):

> Transcription of a gene in the active state is controlled at the stage of initiation, that is, by the interaction of RNA polymerase with its promoter. This is now becoming susceptible to study in the *in vitro* systems . . . ***For most genes, this is a major control point; probably it is the most common level of regulation.*** [page 847, emphasis added].
>
> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that ***the overwhelming majority of regulatory events occur at the initiation of transcription. Regulation of tissue-specific gene transcription lies at the heart of eukaryotic differentiation.*** [pages 847-848, emphasis added]

Thus the question is not whether there is the potential for post-transcriptional regulation of SEQ ID NO:1 expression but whether one skilled in the art would have a reasonable expectation that SEQ ID NO:1 expression correlates with the levels of SEQ ID NO:2 mRNA. Appellants need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner v. Manson*, 383 U.S. 519, 532, 148 USPQ 689 (1966).

In the case of the instant invention, one skilled in the art would be imprudent in assuming, *a*

priori, that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:1 were controlled predominantly in a post-transcriptional manner, thereby dismissing the significance of mRNA levels. Inasmuch as the predictive value of mRNA levels applies to the "utility" of Appellants' invention, Appellants request withdrawal of the rejection.

Appellants note that the specification teaches that Northern analysis reveals the expression pattern of SEQ ID NO:2 which encodes SEQ ID NO:1, in various libraries as shown in Figure 5. In particular, of the 15 tissues which expressed HPAK, six were from the prostate gland and seven were from cancer patients (specification, page 11, lines 17-19).

A careful examination of the tissue libraries listed in Figure 5 indicates the expression of SEQ ID NO:2, by abundance (Abun) and percent abundance (Pct Abun) to be predominantly found in prostate and pancreas tissues. Moreover, expression was noticed in prostate tumor tissue (PROSTUT04), but not in matched non-tumor tissue from the same donor (PROSNOT06). These findings support the teachings of Nakamura, Exhibit H (of record, see response mailed 10/17/02). Nakamura et al. suggest the use of kallikrein 11 and so, SEQ ID NO:1 as a biomarker to distinguish prostate cancer and BPH (see Supplemental Preliminary Remarks submitted 3/19/03, page 7).

The Examiner asserts that Appellants have not shown SEQ ID NO:1 to be an isoform of kallikrein 11, and further suggests that isoforms of a protein have differing, independent expression (Office Action of April 10, 2003, page 18). Even assuming these allegations to be true solely for the sake of argument, they are irrelevant. The use of SEQ ID NO:1 as a biomarker would be found by one of skill in the art to be more likely than not a specific and substantial utility of SEQ ID NO:1 independent of how its expression differs from that of kallikrein 11.

C. Appellants' Evidence that the Claimed HPAK Polypeptide is a Member of the Kallikrein Gene Family Would be Found by One Skilled in the Art to be More Likely Than Not True

There is a substantial likelihood that the HPAK polypeptide shares homology with the kallikrein (serine protease enzyme) gene family, a family in which the members have undisputed utility. Thus, homology can be used to show a substantial likelihood that the claimed polypeptides are similarly useful.

Appellant need not show any more to demonstrate utility.

Evidence of the HPAK polypeptide belonging to the serine protease family of proteins has been established by the homology of SEQ ID NO:1 and 90% variants thereof to other proteins identified as kallikreins. In this regard, HPAK is homologous to two kallikrein polypeptides, human pancreatic kallikrein (SEQ ID NO:3, GI 186653, Specification, page 11, lines 8-10) and kallikrein 11 (Exhibit A, of record, see response mailed 10/17/02, and alignment faxed on 01/28/03). In particular, HPAK shares more than 54% sequence identity with the human pancreatic kallikrein, GI 186653 (See, e.g., Specification, page 11, and Figure 2) and 90% sequence identity with human kallikrein 11, GI 18314498. It is noted that kallikrein 11 is also known as hippostasin, and also known as trypsin-like serine protease (TLSP, PRSS20).

This is more than enough homology to demonstrate a reasonable probability that the utility of the human kallikrein polypeptides can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al. ***supra***. Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to the human kallikrein polypeptides (in particular, kallikrein 11) is, accordingly, very high. Additional studies by others of the serine protease gene family provide further evidence that HPAK is a member of the kallikrein protein family.

1. SEQ ID NO:1 is a Member of the Kallikrein Protein Family

Appellants reiterate their position as stated in the Office Action Response filed October 17, 2002, and the Supplemental Preliminary Remarks filed March 19, 2003. HPAK (SEQ ID NO:1) belongs to the kallikrein family of enzymes, more specifically, SEQ ID NO:1 is a potential splice variant of kallikrein 11. Kallikreins are proteins which function as protease enzymes, more specifically, as serine protease enzymes. These activities are also applicable to the instant invention.

In addition, Appellants submitted the results of a recent BLASTP analysis of SEQ ID NO:1 against the genpept database (Exhibit A, of record). These results corroborate Appellants' assertion

that SEQ ID NO:1 is a novel kallikrein (Specification, page 2, lines 11-13). The BLASTP results provide corroborating evidence in support of Appellants' position that SEQ ID NO:1 is more likely than not a potential kallikrein 11 splice variant. As is evident in Exhibit A, HPAK is 90% (human, GI 18314498) identical to the kallikrein 11 (TLSP) as analyzed by Yousef et al. (Yousef, G.M. et al. (2000) Genomics 63:88-96, Attachment F, of record). Such high sequence identity clearly indicates to one of skill in the art that HPAK is a potential splice variant of kallikrein 11.

Examination of the sequence alignment faxed to the Examiner on January 28, 2003, revealed that HPAK had **100% identity** with human kallikrein 11 sequences as presented in Exhibit A (of record, from residue L61 to N253 (numbering on SEQ ID NO:1).

Appellants reiterate for the Board's convenience evidence identifying residues within SEQ ID NO:1 and kallikrein 11 which constitute the trypsin-like serine protease domain, as provided in Exhibit C (submitted in the October 17, 2002 response):

> Serine protease enzymes, including the instant invention of SEQ ID NO:1, are further identified by functional motifs, domains and sites indicative of biological activity. Exhibit C represents the likely trypsin-like serine protease (Tryp_SPc) and trypsin (trypsin) domains within SEQ ID NO:1.
>
> The first alignment is SEQ ID NO:1 (Query; residues R21 to I243) aligned with a representative trypsin-like serine protease domain comprising 230 amino acid residues (Sbjct, gnl|CDD|7285).... One of ordinary skill in the art would interpret the identification of both trypsin-like serine protease and trypsin domains within SEQ ID NO:1 as evidence that more likely than not, SEQ ID NO:1 would also have protease activity because SEQ ID NO:1 has the functional domains necessary for protease activity.

Clearly, one of ordinary skill in the art would conclude based on Appellants' evidence that SEQ ID NO:1 has the trypsin-like serine protease domain and so, more likely than not, possesses serine protease activity.

2. Sequence Homology is a Method for Sequence Identification That is Recognized and Well-Accepted in the Art

Further, applying the teachings of Brenner et al. *supra*, the sequence homology of SEQ ID NO:1 in excess of 40% over many more than 70 amino acid residues, strongly supports Appellants'

position that the claimed polypeptide is related to the human kallikrein polypeptides. Since the criteria of Brenner et al. are based on a data set of known homologous proteins with shared structural and functional features, one of ordinary skill in the art would reasonably expect the claimed polypeptides of the invention possess the evolutionarily conserved **structural and functional** characteristics of kallikreins. Indeed, SEQ ID NO:1 possesses the structural characteristics and more likely than not, the functional properties of the kallikrein family of proteins.

It is known in the art that natural selection acts to conserve protein function. Conversely, mutations that reduce or abolish protein function are usually eliminated by natural selection. Based on these central tenets of molecular evolution, Appellants put forth that the amino acid differences between the claimed polypeptide and the known kallikreins are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would therefore conclude that, more likely than not, the level of conservation observed between Appellants' polypeptide and the human kallikreins are indicative of a common function, and hence common utility, among these proteins. Such high sequence identity and the presence of the trypsin-like serine protease domain which is characteristic of serine protease family members, clearly indicates to one of ordinary skill in the art that HPAK is more likely than not a potential splice variant of kallikrein 11 having serine protease activity. Therefore, the teachings of Yousef et al. are also applicable to HPAK.

Evidence of the instant invention belonging to the kallikrein family of proteins has been established by the homology of SEQ ID NO:1 to other proteins identified as kallikreins. Therefore, homology **can** and **is** being used by Applicant to show that there is a strong and substantial likelihood that the claimed polypeptides are similarly useful. Appellants need not show any more to demonstrate utility.

D. Kallikrein Proteins Belong to the Serine Protease Gene Family, a Gene Family Known to Have Identifiable Structural Characteristics and Well-Established Utilities

The kallikrein proteins, like SEQ ID NO:1, are unique members of the serine protease gene

family. Kallikreins, as serine proteases, function in the selective cleavage of high-molecular-weight substrates and release of peptides with potent biological activity (Exhibit F, p. 88, of record, see response filed October 17, 2002). Kallikreins are characterized by the presence of the catalytic triad, comprised of three amino acids: H62, D110 and S203 (numbering on SEQ ID NO:1), as well as the presence of conserved amino acid motifs surrounding each amino acid residue of the catalytic triad: WLLTAA$\underline{H}_{62}$C; $\underline{D}_{110}$IMLV; and GD$\underline{S}_{203}$GGP0L. Additionally, the presence of 10 conserved cysteine residues and a D_{200} amino acid residue are also characteristic of serine proteases in general, and the kallikrein gene family in particular. Kallikrein 11, and so too, SEQ ID NO:1, contains the typical catalytic triad of serine proteases, H_{62}, D_{110} and S_{203}, as well as the conserved peptide motif around each amino acid of the catalytic triad (WLLTAA**H**C (WFLTAA**H**C in SEQ ID NO:1), **D**IMLV, and GD**S**GGPL), 10 conserved cysteine residues and D200 (Exhibit F, p. 92, Specification, page 1, lines 16-18, and page 11, lines 10-16).

The foregoing evidence provides compelling support for Appellants' assertions that like kallikrein 11, SEQ I D NO:1 would also be expected to both have serine protease activity and be a novel splice variant of kallikrein 11

1. Sequence Motifs Characteristic of Serine Proteases Are Also Found Within SEQ ID NO:1

a. The Catalytic Triad

As discussed at length previously (see, e.g., Supplemental Preliminary Amendment filed 3/19/03, page 6 and page 8; Exhibit F, Figure 5, page 93 and Exhibit K, pages 187-188, both Exhibits having been submitted on 10/17/02), the amino acid residues comprising the catalytic triad are located within SEQ ID NO:1 at His65, Asp112 and Ser206. Thus, SEQ ID NO:1 has the conserved amino acid residues which comprise the catalytic triad identified within kallikreins, His65, Asp112 and Ser206.

b. Conserved Regions Around the Catalytic Triad

The Examiner continues to maintain that "SEQ ID NO:1 does not have the "consensus" sequence of different members of the kallikrein family" (Office Action of September 8, 2003, page 3). Appellants suggest that the Examiner has misunderstood the conservation of amino acid residues around

the catalytic triad within kallikreins and more broadly, within serine protease proteins. The Examiner further asserts that "even one amino acid in this important consensus sequence in the critical catalytic triad of different members of kallikrein family is unpredictable." Appellants respectively point out that generally a consensus sequence as would be understood by the skilled artisan allows for some variation. Thus, The Examiner's allegation that a single amino acid change may produce an unpredictable result in a consensus sequence is not always true. Sequences used to establish a 'consensus sequence' are understood to have differences. Therefore, a single amino acid change would not be considered by one of skill in the art to necessarily result in an unpredictable change of protein function. The Examiner's reasoning is nothing more than pure argument, and fails to establish or support a *prima facie* finding of non-utility for SEQ ID NO:1. No evidence specific to kallikrein proteins in general or the claimed polypeptide sequences in particular, has been proffered.

The Examiner describes numerous references (Lazar et al., Burgess et al., Ohannesian et al., and Assemat et al.) intimidating that a single amino acid change "could change the properties or activities of the protein" (Office Action of September 9, 2003, page 3). However, none of these concern serine proteases or kallikrein.

In contrast, Exhibit K teaches highly conserved regions around the catalytic triad: WVLTAAHC, DLMLL, and GDSGGPL (Exhibit K, of record, pages 187-188). Additionally, Appellants have specified the conserved regions within SEQ ID NO:1 around the catalytic triad: WFLTAAHC, DIMLV, GDSGGPL, i.e., His65, Asp112 and Ser206 (Preliminary Amendment filed 3/19/03, page 8).

Upon examination of the amino acid residues surrounding the catalytic triad of SEQ ID NO:1, it is readily apparent that SEQ ID NO:1 has the conserved sequences of DIMLV and GDSGGPL and has the difference of a single amino acid in the first catalytic triad, WFLTAAHC. Appellants assert that: i.) a single amino acid change within the region around the catalytic triad of SEQ ID NO:1 does not change the activity of a serine protease enzyme; ii.) the catalytic triad; H65, D113 and S206 are highly indicative of serine protease activity; and iii.) the trypsin-like serine protease (Tryp_SPc) domain is recognized in the art as the region within serine protease enzymes which provides enzymatic activity.

i. Amino Acid Differences Within the Region Around the Catalytic Triad Do Not Negate Serine Protease Activity

In rebuttal to the Examiner's alleged unpredictable effect of a change in an amino acid residue in the region surround the catalytic triad, Appellants submit herewith, Attachment L, an alignment of several human kallikreins as well as serine proteases from other organisms. The submission of such evidence is necessitated by the Examiner presenting for the first time in the Office Action of Septermber 8, 2003, the argument that the sequences flanking the catalytic triad do not follow a consensus sequence (Office Action of September 8, 2003, page 3). Appellants have only suggested that there was a conserved sequence flanking the catalytic triad, not that there was a definitive consensus sequence. The following is a list of representative serine protease enzymes are aligned in Attachment L:

SEQ_ID_NO_1 [Homo sapiens]
g8574439 prostate-type hippostasin [Homo sapiens]
g6681454 Hippostasin [Homo sapiens]
g5713131 trypsin-like serine protease [Homo sapiens]
g5919239 kallikrein-like protein 3 [Homo sapiens]
g10799394 kallikrein 9 [Homo sapiens]
g6063386 kallikrein-like protein 4 KLK-L4 [Homo sapiens]
g10799398 kallikrein 13 [Homo sapiens]
g6715552 kallikrein-like protein 6 [Homo sapiens]
g13897995 kallikrein 14 [Homo sapiens]
g1552516 trypsinogen C [Homo sapiens]
g4589283 kallikrein-like protein 2 KLK-L2 [Homo sapiens]
g31075483 kallikrein 5 splice variant 2 [Homo sapiens]
TRY5_AEDAE/12-232 [Aedes aegypti]
CTRL_HALRU/24-251 [Haliotis reufescens]
SP1_RARFA/205-391 {Rarobacter faecitabidus]

The three amino acids which comprise the catalytic triad are represented in Attachment L (designated "*") on pages 4 of 6 and 5 of 6 (beginning with the third sequence alignment block on page 4 of 6), "E22," the first amino acid of the first line, third block reading "ENKIIGGHT" (g6715552) and "VITAAHCG" the last eight amino acid residues, first line of the third block.

Examination of pages 4 of 6 and 5 of 6 of Attachment L (the third alignment block, the sequence alignments continue on page 5 of 6) illustrate not only single amino acid residue differences

around H65 (numbering corresponding to SEQ ID NO:1, (e.g., g6063386, W–FLTAAHC and g10799394 read W–LLTAAHC), but two differences (e.g., g6715552 and g13897995, W–VITAAHC, CTRL_HALRU reads K–ALTAAHC) and three differences (e.g., TRY5_AEDAE reads W–VMTAGHC and SP1_RARFA reads GFLTAGHC, sequence differences underlined). In particular, the second amino acid residue of the conserved region around H65 (WVLTAAHC), i.e., valine (V), is shown to be either: 1.) leucine (L), a conservative amino acid substitution for valine (Kallikeins 11, 3, 2, 5); 2.); phenylalanine (F), for which leucine is a conservative amino acid substitution (SEQ ID NO:1, SPI_RARFA/205-391); or 3.) alanine (A), which is not a conservative substitution for L, V or F (CTRL_HALRU). Clearly amino acid residues flanking the catalytic triad are different within serine proteases in general and in particular, within the kallikrein family.

Appellants respectfully emphasize that: 1) none of the proteins of kallikreins, 2, 3, 5, 11, SPI_RARFA/205-391 and CTRL_HALRU are 100% identical to the amino acids surrounding the H65 residue, the first member of the catalytic triad within SEQ ID NO:1 or when comparing the surrounding residues of each about their H residue of the catalytic triad; 2) despite differences within the amino acid sequences surrounding the H residue of the catalytic triad, each of the proteins retains serine protease activity; and 3) the catalytic triad is conserved throughout the serine protease family of enzymes. Thus, one of skill in the art would interpret such evidence to indicate that it is the presence of the three amino acid residues comprising the catalytic triad that are directly indicative of serine protease activity and that the amino acid sequences flanking each of the three residues which comprise the catalytic triad are not directly related to the proteins functioning as serine proteases.

ii. The Catalytic Triad is Highly Indicative of Serine Protease Activity

The conservation of the catalytic triad within a variety of serine proteases from divergent organisms strongly suggests to the skilled artisan the importance of the catalytic triad in maintaining serine protease activity. Conversely, the lack of conservation of the amino acid residues surrounding the catalytic triad, especially H65, are less significant to the maintenance of serine protease activity.

iii. The Trypsin-like Serine Protease (Tryp_SPc) Domain Is the Enzymatic Active Site for Serine Protease Enzymes

The Examiner notes "even if these regions are trypsin-like serine protease domain or trypsin domain of the trypsin-like serine protease or trypsin, respectively, which confer the protease activity, it is noted that there are several differences in several amino acids at various positions between SEQ ID NO:1 and the trypsin-like serine protease domain or trypsin domain" (Office Action of April 10, 2003, page 17). The Examiner is referring to Exhibit C (see response filed 10/17/02), a comparison of the trypsin-like serine protease and trypsin domains identified as such within kallikrein 11, as so, more likely than not, within SEQ ID NO:1 too.

Appellants respectfully bring to the attention of the Board that the Examiner's unfamiliarity with the most basic amino acid sequence analysis and comparison programs apparently renders much of the evidence submitted by Appellants difficult to comprehend by the Examiner. The Examiner has, to her credit, exhibited great determination and effort in attempting to understand the evidence submitted. However, the alignments presented in Exhibit C were generated at the National Center for Biotechnology Information (NCBI) of the National Library of Medicine at the National Institutes of Health, Bethesda, MD. NCBI is recognized internationally and nationally as the repository for GenBank, a DNA database, as well as for the sequence analysis suite of programs known as Entrez. Exhibit C is a result of an NCBI developed amino acid sequence database and analysis program entitled "Conserved Domain Database (CDD). CDD consists of NCBI identified functionally conserved domains in order to identify comparable domains in other species and organisms. Thus, not only are the sequences shown in Exhibit C to which Kallikrein 11 is compared involved in conferring serine protease activity, but the "differences" noted by the Examiner are the result of making a comparison to a consensus sequence representing a conserved domain having serine protease activity.

A trypsin-like serine protease consensus sequence, by definition, is a compilation of representative sequences, each having a trypsin-like serine protease domain and experimentally determined proteolysis activity. Thus, one of ordinary skill in the art would utilize the information in Exhibit C for the identification of a trypsin-like serine protease domain within kallikrein 11 and so, too, within SEQ ID NO:1. The trypsin-like serine protease domain consensus sequence, as provided in

Exhibit C would not be expected by one of ordinary skill in the art to be 100% identical to SEQ ID NO:1. Therefore, one of ordinary skill in the art, upon the identification within SEQ ID NO:1 of: i) a trypsin-like serine protease domain; ii) the catalytic triad; and iii) the residues surrounding the catalytic triad, would conclude that more likely than not that SEQ ID NO:1 would more likely than not also have serine protease activity. Therefore, not only are the amino acid differences insufficient to provide conclusive evidence that kallikrein 11 lacks serine protease activity, one of skill in the art would find the identification of such domains within kallikrein 11 and so too, within SEQ ID NO:1, indicative of serine protease activity within SEQ ID NO:1.

III. The Diagnosis of Acquired and Inherited Disease, Expression Profiling, and Drug Development are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

A. The uses of the claimed HPAK polypeptides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene and protein expression profiling. These uses are explained in detail in the previously filed Furness Declaration. The claimed polypeptide is a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity. The claimed methods are useful to perform gene expression analysis using cDNA microarrays.

The instant application is a divisional of, and claims priority to, United States patent application Serial No. 08/790,137 filed on January 29, 1997 (hereinafter "the Hillman '187 application"), both having the identical specification.

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Hillman '187 application on April 8, 1997 would have understood that application to disclose the claimed HPAK polypeptide to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 10-13). Much, but not all, of

Mr. Furness' explanation concerns the use of the claimed polypeptide in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. (Furness Declaration at ¶ 10.)

The claimed polypeptide makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Hillman '187 application,. . . and other related pre-April 8, 1997 publications, persons skilled in the art on April 8, 1997 clearly would have understood the Hillman '187 application to disclose the SEQ ID NO:1 polypeptide and the SEQ ID NO:1 variant to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity. . . (Furness Declaration, ¶ 10)
>
> * * *
>
> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the sequence of the SEQ ID NO:1 polypeptide and/or the SEQ ID NO:1 variant would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating inflammation and disorders associated with cellular development, proliferation and differentiation for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, page 26).

The Patent Examiner contends that the claimed HPAK polypeptide (and claimed methods) cannot be useful without precise knowledge of the function of the HPAK polypeptide. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

B. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Furness in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (of record):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. ((Reference of record, see Response to Office Action, filed April 9, 2001), page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (References of record, see Response to Office Action, filed April 9, 2001).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference of record, see Response to Office Action, filed April 9, 2001). Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

The specification teaches that HPAK is a member of the kallikrein gene family and that kallikreins are useful in the diagnosis, prevention and treatment of cancer and disorders of the prostate (see specification, page 2, lines 6-8). Appellants have presented evidence that the claimed

polypeptides would have the utilities of kallikrein proteins, proteins which are known to be involved in cancer and prostate disorders. Therefore, one of ordinary skill in the art would conclude it is likely that HPAK would also have these uses. Thus, the claimed invention meets the utility requirements under 35 U.S.C. §§ 101 and 112, first paragraph.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

C. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polypeptide, the databases become even more

powerful tools. Thus, the claimed invention adds more than incremental benefit to the drug discovery and development process.

IV. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that "there is no indication that SEQ ID NO:1 has serine protease activity" the claimed polypeptide [and] variants lack "specific and substantial" utility. (Final Office Action at pp. 3-4). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role or Function of an Expressed Polypeptide is Not Required to Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 10-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed polypeptide, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite evidence that the claimed polypeptide is a member of the kallikrein polypeptide family, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the kallikrein polypeptide family to HPAK. In the Office Action of July 17, 2002, the Patent Examiner takes the position that:

> SEQ ID NO:1 has not been shown to be functionally related to a human pancreatic kallikrein. . . . neither the specification, nor the art of record teaches any association of SEQ ID NO:1 with a protease or chymotrypsinogen activity. . . .no indication that these three non-contiguous conserved amino acids and said amino acid D200 would confer serine protease activity to SEQ ID NO:1. . . .no indication that these cysteines would form disulfide bonds in SEQ ID NO:1. . . . no indication that said conformation would confer serine protease activity to SEQ ID NO:1. . . . one could not predict that the claimed SEQ ID NO:1 has the same function as a human pancreatic kallikrein, based

on the teaching of Bowie et al., Lazar et al., Burgess et al., and Bork. (Office Action of July 17, 2002, pages 6-7).

To demonstrate utility by membership in the class of kallikrein polypeptides, the Examiner would require that all kallikrein polypeptides possess a "common" utility.

The Examiner has not provided any evidence that any member of the kallikrein polypeptide family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the kallikrein polypeptide family, useful.

Even if the Examiner's "common utility" criterion were correct, the kallikrein polypeptide family would meet it. It is undisputed that known members of the kallikrein polypeptide family function as a serine proteases. A person of ordinary skill in the art need not know any more about how the claimed invention functions as a serine protease to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given kallikrein polypeptide functions as a serine protease. The Examiner then goes on to assume that the only use for HPAK absent knowledge as to how this member of the kallikrein polypeptide family actually works is further study of HPAK itself. However, this assumption is incorrect.

As disclosed by Appellants, knowledge that HPAK is a kallikrein-like polypeptide is more than sufficient to make it useful for conducting protein expression monitoring studies on proposed (or actual) drugs for treating cancer and disorders of the prostate. Indeed, HPAK has been shown to be expressed in breast, prostate and cancerous prostate cDNA libraries. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

C. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt Appellants' *Prima facie* Case of Homology as an Acceptable Assertion of Utility for the Claimed Invention

Appellants have shown that HPAK shares homology with the kallikrein gene family, a family

consisting of members known to have undisputed utility, and therefore, homology can be used to show a substantial likelihood that the claimed polypeptide is similarly useful. Appellant need not show any more to demonstrate utility. Specifically, the kallikrein family includes GI 186653, a human pancreatic kallikrein (KLK1), which shares about 54% sequence identity with HPAK (Specification, page 11). Human KLK1 has been demonstrated *in vivo* to release (by proteolysis) lysyl-bradykini (kallidin) from low molecular weight kininogen (Exhibit K, p. 195, of record). Moreover, SEQ ID NO:1 is 90% identical with human Kallikrein 11 as discussed above.

Under the applicable law, once the Applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided any evidence to doubt the utility of any member of the kallikrein gene family, let alone a substantial number of those members.

Thus, the preponderance of the evidence supports the reasonable probability that the HPAK claimed polypeptides are, in fact, members of the kallikrein gene family of enzymes, which are known to have specific utility. Moreover, HPAK contains a 24 amino acid signal sequence, the catalytic triad, H65, D113, and S206 (numbering according to SEQ ID NO:1), the conserved amino acids around the catalytic triad, 10 conserved cysteine residues for disulfide bond formation, D200 which likely confers chymotrypsinogen-like activity (specification, page 11, lines 10-16), and the trypsin-like serine protease domain, all being properties which are characteristic of serine proteases and so serine protease activity. Therefore, the Examiner must accept Appellants' demonstration by homology that the HPAK polypeptide is a member of the kallikrein gene family of serine proteases and the asserted utility.

Appellants note for the benefit of clarification, that the trypsin-like serine protease domain represents a consensus sequence of a trypsin-like serine domain. Being that the domain represents a consensus sequence derived from numerous trypsin-like serine protease domains across a variety of species, one of ordinary skill in the art would accept the identification of such a domain within SEQ ID NO:1 as evidence that said domain resides within SEQ ID NO:1, especially in view of the presence of the catalytic triad, H65, D113, and S206 (numbering according to SEQ ID NO:1), and D200 within

said domain. Contrary to the assertion of the Examiner that "there are several differences in several amino acids at various positions between SEQ ID NO:1 and the trypsin-like serine protease or trypsin domain" (Office Action of April 10, 2003, page 17), one of skill in the art would understand such differences to be a given consequence of the construction of a consensus sequence. Appellants once again refer to Attachment L, pages 4 of 6 and 5 of 6. It is readily apparent that the trypsin-like serine protease domain is present within the kallikreins and serine protease proteins represented, each having numerous amino acid differences within the trypsin-like serine protease domain consensus sequence, and yet, serine protease activity is not in doubt. Therefore, the identification of the trypsin-like serine protease domain within kallikrein 11/SEQ ID NO:1 as shown in Exhibit C, would further lead one of ordinary skill in the art to conclude that more likely than not that SEQ ID NO:1 has serine protease activity.

In addition, it appears from the statements of by the Examiner that Appellants are being required to assert a rigorous correlation to establish the identity of HPAK as a member of the kallikrein gene family as well as to establish a specific disease affected by HPAK. However, the final Utility Examination Guidelines provides that

> [A] "rigorous correlation" need not be shown in order to establish practical utility; "reasonable correlation" is sufficient. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed Cir. 1996).

Appellants have provided sufficient evidence to establish a "reasonable" correlation.

V. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent

disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § IV.B. (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § IV.B. Thus, the Training Materials cannot be applied consistently with the law.

VI. Conclusion

Appellants have provided evidence that homology can be used to demonstrate utility. Further, persons skilled in the art would have considered the HPAK polypeptide to be a kallikrein protein and member of the serine protease family of enzymes. Moreover, the Specification teaches that SEQ ID NO:1 has homology to proteins identified as kallikreins. Specifically, to human pancreatic kallikrein (GI 186653; SEQ ID NO:3) and African rat renal kallikrein (GI 55527; SEQ ID NO:4). HPAK has chemical and structural characteristics conserved between HPAK and kallikrein proteins such that one

skilled in the art would conclude that more likely than not HPAK is also a kallikrein protein and member of the kallikrein gene family of serine protease proteins. Additionally, Mitsui et al. (of record, Exhibit G, see response filed 10/17/02) have determined that kallikrein 11/HPAK is expressed and has serine protease activity. Accordingly, Appellants have established, and one of ordinary skill in the art would find Appellants' evidence more reasonable than not, that the HPAK polypeptide is a member of the kallikrein gene family of serine protease proteins and that HPAK functions as a serine protease protein. Appellants have disclosed the claimed invention in sufficient detail and provided identifying characteristics such that the skilled artisan would know how to use the claimed invention in the detection of HPAK polypeptides and in the diagnosis, prevention, and treatment of cancer and disorders of the prostate.

Thus, for all the above reasons, the claimed HPAK polypeptides have well-established utilities and/or the Specification provides asserted specific, substantial and credible utilities. Therefore, Appellants respectfully request reversal of the rejection based on 35 U.S.C. §101.

ISSUE 3: To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

ISSUE 4: The Rejection under 35 U.S.C. §112, first paragraph is Improper Because All of the Claimed 90% Variants of SEQ ID NO:1 are Sufficiently Enabled

Claims 1 and 18-20 stand rejected under the first paragraph of 35 U.S.C. §112 because the specification allegedly does not describe how to make and use the claimed variants of SEQ ID NO:1. This rejection is traversed.

Claim 1 recites:

1. An isolated polypeptide selected from the group consisting of:
a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, and
b) a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:1 over the entire length of SEQ ID NO:1, said polypeptide having serine protease activity.

The Examiner has asserted, *inter alia*, that "SEQ ID NO:1 has not been shown to have serine protease activity" (Office Action of September 8, 2003, page 5), and that "SEQ ID NO:1 has not been **convincingly** demonstrated to be a serine protease" (Office Action of April 10, 2003, page 23) (emphasis added).

Appellants note that while an asserted utility must be described with specificity, the patent applicant need not demonstrate utility "convincingly," that is, to a certainty or a "truth or reality of something."

Appellants' representatives reiterate that during the interview of May 6, 2003, it was Appellants' representatives' understanding that Examiner Davis, together with SPE Anthony Caputa, concurred in the finding that Appellants had indeed discovered a novel serine protease enzyme. Further, they concurred that the novel polypeptide is likely a member of the kallikrein gene family, and, specifically, is likely to be a splice-variant of the kallikrein 11 protein. Moreover, they concurred that Appellants' claims to 90% variants of SEQ ID NO:1 encompassed kallikrein 11. Kallikrein 11 is known to one of skill in the art to have serine protease activity and be a potential biomarker for prostate and breast cancers, *supra*. This matter should no longer be at issue.

A. The Legal Standard for Enablement

The Examiner has also asserted, *inter alia*, that "the claimed 90% variants encompass kallikrein 11, however, Applicant has not disclosed how to make the claimed variants that have serine protease activity. That is, in the specification and the claims it has not been shown which sequence of SEQ ID NO:1 confers serine protease [activity], such that one can make a variant of SEQ ID NO:1 that has serine protease activity" (pages 3-4) (emphasis in original).

The legal standard for enablement is a well-settled issue. For example, in *Hybritech Incorporated v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (CAFC 1986), the court stated that:

> Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention, *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960, 220 USPQ 592, 599 (Fed. Cir. 1983), is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive...a patent need not teach, and preferably omits, what is well known in the art. *Lindemann*, 730 F.2d at 1463, 221 USPQ at 489.

In the present case, the Specification discloses how to make polypeptides which are 90% identical to SEQ ID NO:1 and have serine protease activity (See, e.g., Sequence Listing, and specification, page 16, line 9 through page 23, line 13).

B. Making Polypeptides Which are 90% Identical to the Sequence of SEQ ID NO:1 Over the Entire Length of SEQ ID NO:1 and Having Serine Protease Activity is Well Within the Knowledge of Skilled Artisans

Appellants submit that the making of 90% variants of a serine protease enzyme, including 90% variants of SEQ ID NO:1 having serine protease activity use methods well known to the skilled artisan and are so recognized by the USPTO as stated in the USPTO's own training materials for implementation of the Written Description Guidelines under 35 U.S.C. § 112, first paragraph. In the "Synopsis of Application of Written Description Guidelines" (USPTO Website www.uspto.gov, March 1, 2000), at page 53 of these guidelines, a claim to "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B" is considered to meet the written description requirements because:

> --- ***procedures for making variants of SEQ ID NO:3 are conventional in the art*** and an assay is described which will identify all other proteins having the claimed catalytic activity. Moreover, ***procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art.*** (emphasis added)

The Guidelines further state:

> The single species disclosed (SEQ ID NO:3) is representative of the genus because ***all members have at least 95% structural identity with the reference compound*** and because of ***the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity***. (emphasis added)

Thus, just as procedures for making 95% variants of SEQ ID NO:1 are recognized by the USPTO for being conventional in the art, these same procedures would be used to produce 90% variants of SEQ ID NO:1. Likewise, just as the assay in Example IX, page 44 of the specification can identify variants at least 95% identical to a single species (SEQ ID NO:1), having serine protease activity, so too can the assay of Example IX identify 90% variants of SEQ ID NO:1 having serine protease activity.

One of ordinary skill in the art would use methods for the construction of 90% variants which are conventional in the art, and the assay of Example IX to identify those 90% variants of SEQ ID NO:1 which have serine protease activity. Such experimentation is routine in the molecular biology arts. The disclosure by Appellants of a "sequence" which confers serine protease activity is not possible, as serine protease activity is a property of a domain within a polypeptide sequence and such domains are well known in the art. Thus, "a patent need not teach, and preferably omits, what is ***well known*** in the art. *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

Appellants note that a sequence cannot confer an enzymatic activity. Therefore, the specification and the claims need not show which "sequence" confers serine protease activity, as one of ordinary skill in the art would use conventional means to make polypeptides at least 90% variants to SEQ ID NO:1 and assay for serine protease activity using the method taught in Example IX of the specification.

C. Evidence Cited by the Examiner Does Not Make a *Prima facie* Case for Lack of Enablement

The Examiner has cited Lazar et al., Burgess et al., Ohannesian et al., and Assemat et al. in support of the position that a single amino acid difference in the "consensus sequence" around the catalytic triad of kallikrein family members is unpredictable (Office Action of September 8, 2003, page

5). Appellants position is that Lazar et al., Burgess et al., are not applicable for reasons already of record in the response filed April 9, 2001. Moreover, neither Ohannesian et al. nor Assemat et al. are applicable to the instant invention as claimed. 90% variants of SEQ ID NO:1 are those having serine protease activity. Ohannesian et al. is directed to an amino acyl-tRNA synthetase and Assemta et al. exemplifies a thioredoxin. Therefore, Ohannesian et al., and Assemat et al. are not applicable to the claimed invention.

The Examiner has also asserted, *inter alia*, that claims 1, 20 and 26 (claim 26 has been deleted) read on naturally-occurring allelic variants of SEQ ID NO:1. The Examiner continues:

> Thus the scope of the claims includes numerous structural variants that would exist in nature. No common structural attributes that identify the claimed variants are disclosed, because the function of SEQ ID NO:1 has not been convincingly demonstrated to be a serine protease . . . (Office Action of April 10, 2003, page 23).

The Examiner has cited Burgess et al., Lazar et al., Tao et al. (J. Immunol. (1989) 143:2595-2601; of record), and Gillies et al. (Hum. Antibodies Hybridomas (1990) 1:45-54; of record) as demonstrating that even a single amino acid change can dramatically affect protein activity and attributes of a protein. However, these references are not relevant to the case at hand. Lazar et al. describe the mutagenesis of two amino acid residues that are highly conserved between EGFs and TGF-αs. Similarly, Burgess et al. describe mutagenesis of HBGF-1 at an amino acid residue known to be important for ligand binding. Tao et al. and Gillies et al. describe how a glycosylation of antibodies reduces resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies. In all of these cases, the function of the polypeptide has been altered by single amino acid mutations or chemical modifications, but that function has not been entirely eliminated. Therefore, one of skill in the art would still be able to use these altered polypeptides **in the exact same manner as one would use the non-altered polypeptides**, even though the results would not be exactly the same as if the non-altered polypeptides were used. Likewise, one of skill in the art would know how to use the recited variants of SEQ ID NO:1; even if the results achieved from using the recited variants were not equivalent to the results achieved from using the SEQ ID NO:1 polypeptide, one of skill in the art would still be able to achieve **some** level of results by using the recited variants in

the same manner as the SEQ ID NO:1 polypeptide. This is all that is required to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

The Examiner continues, asserting that how nature has determined which amino acids are substituted, deleted or added in the claimed variants has not been disclosed in the specification, suggesting that the process of natural selection is unpredictable. The Examiner suggests that the result would be a "vast number of unrelated sequences of unknown function" would result from using hybridization or PCR techniques (Office Action of September 8, 2003, pages 5-6). Appellants disagree for the following reasons.

D. Naturally Occurring Polypeptide Variants Occur in Nature

The Examiner has also asserted, *inter alia*, that the Specification provides insufficient guidance for one of skill in the art to "obtain naturally-occurring allelic variants of SEQ ID NO:1" (Office Action of April 10, 2003, page 22). Note, however, that the claims recite not only that the polypeptides have at least 90% sequence identity to SEQ ID NO:1, but also have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate amino acid sequences.

The claims define the variant polypeptides as "naturally occurring" and being at least 90% identical to the amino acid sequence of SEQ ID NO:1. The existence of such variants is made by nature; and "naturally occurring" polypeptide variants occur in nature. The Specification teaches how to find polynucleotide variants (See, e.g., page 33, lines 10-30) which can then be expressed to make polypeptide variants. The Specification also teaches how to use antibodies to purify naturally occurring HPAK (See, e.g., page 45, lines 16-26). The scope of the polypeptide variants to which the claimed antibodies specifically bind is described by the phrase "at least 90% identical to the sequence of SEQ ID NO:1." The Specification describes how to use BLAST to determine whether a given sequence falls within the "at least 90% identical" scope (See, e.g., page 39, lines 5-18). In addition, determination of percentage identity is well known in the art. Moreover, the "comprising" language used to define the variant polypeptides does not preclude the ability to make the claimed subject matter. The term

"comprising" as used in the Specification merely encompasses, for example, fusion proteins which contain the variant sequences (See, e.g., page 15, lines 12-14; page 16, lines 2-4). Methods for making fusion proteins are well known in the art.

Given the information provided by SEQ ID NO:1 (the amino acid sequence of HPAK) and SEQ ID NO:2 (the polynucleotide sequence of HPAK), one of skill in the art would be able to routinely obtain "a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:1 over the entire length of SEQ ID NO:1, said polypeptide having serine protease activity." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, *e.g.*, page 33, lines 10-22; and Example VI at page 43. In particular, "the stringency of the hybridization or amplification (maximal, high, intermediate, or low) will determine whether the probe identifies only naturally occurring sequences encoding HPAK, alleles, or related sequences" (specification, p. 33 lines 12-17).

One skilled in the art employing maximal or high conditions of stringency in the hybridization or amplification method would reasonably expect that only naturally occurring sequences encoding HPAK and at least 90% variants thereof would more likely than not be detected. Such experimentation is considered routine in the art for the identification of functional equivalents of HPAK and 90% variants thereof and would not be expected to result in vast numbers of unrelated sequences of unknown function.

Because the sequences are naturally occurring, nature routinely only conserves functional proteins and variants thereof. To suggest otherwise reviles the central tenant of biology, any viable organism remains viable because it produces only what it needs and can use to ensure its continued survival and existence, e.g.., its expressed proteins. A nonfunctional protein would not always result in continued survival of the organism. Nature selects only those gene products which maintain the existence of the organism and any nonfunctional gene would be eliminated through the process of natural selection. Thus, under maximal and high stringency hybridization or amplification conditions, and following the teachings of the specification, one of ordinary skill in the art would more likely than not detect a relatively

small number of similarly related sequences. Therefore, one skilled in the art, following the teachings of the specification, need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library under controlled hybridization conditions or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited variants of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited variants of SEQ ID NO:1.

Accordingly, the Specification would allow one of skill in the art to practice the full scope of what is claimed. Reversal of this rejection is therefore requested.

(9) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax,"[1] to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Due to the urgency of this matter and its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate.

---

[1]"The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

Respectfully submitted,

INCYTE CORPORATION

Date: 10, March 2004

Shirley A. Recipon
Reg. No. 47,016
Direct Dial Telephone: (650) 621-8555

Date: 10 March 2004

Cathleen M. Rocco
Reg. No. 46,172
Direct Dial Telephone: (650) 845-4587

3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

Attachment L: Clustal W alignment of Serine protease proteins.

APPENDIX - CLAIMS ON APPEAL

1. An isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, and

b) a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:1 over the entire length of SEQ ID NO:1, said polypeptide having serine protease activity.

18. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:1.

19. A composition comprising a polypeptide of claim 18 and a suitable pharmaceutical carrier.

20. A composition comprising a polypeptide of claim 1 and a suitable pharmaceutical carrier.

SeqServer®
biology *in silico*

ClustalW Results

Sequences | Help

Retrieval | BLAST2 | FASTA | ClustalW | GCG Assembly | Phrap | Translation

 SeqServer Version 4.6 Jan 2002

- g5919239
- g10799394
- g6063386
- g10799398
- g6715552
- g13897995
- g1552516
- g4589283
- g31075483
- SEQ_ID_NO_1
- TRY5_AEDAE/12-232
- CTRL_HALRU/24-251
- SP1_RARFA/205-391

```
CLUSTAL W (1.7) Multiple Sequence Alignments


Sequence format is Pearson
Sequence 1: g5919239              250 aa
Sequence 2: g10799394             250 aa
Sequence 3: g6063386              277 aa
Sequence 4: g10799398             277 aa
Sequence 5: g6715552              251 aa
Sequence 6: g13897995             251 aa
Sequence 7: g1552516              247 aa
Sequence 8: g4589283              293 aa
Sequence 9: g31075483             293 aa
Sequence 10: SEQ_ID_NO_1          253 aa
Sequence 11: TRY5_AEDAE/12-232    238 aa
Sequence 12: CTRL_HALRU/24-251    254 aa
Sequence 13: SP1_RARFA/205-391    525 aa
Start of Pairwise alignments
```



```
Aligning...
Sequences (1:2) Aligned. Score:  100
Sequences (1:3) Aligned. Score:  43
Sequences (1:4) Aligned. Score:  43
Sequences (1:5) Aligned. Score:  44
Sequences (1:6) Aligned. Score:  44
Sequences (1:7) Aligned. Score:  38
Sequences (1:8) Aligned. Score:  44
Sequences (1:9) Aligned. Score:  44
Sequences (1:10) Aligned. Score:  51
Sequences (1:11) Aligned. Score:  28
Sequences (1:12) Aligned. Score:  23
Sequences (1:13) Aligned. Score:  7
Sequences (2:3) Aligned. Score:  43
Sequences (2:4) Aligned. Score:  43
Sequences (2:5) Aligned. Score:  44
Sequences (2:6) Aligned. Score:  44
Sequences (2:7) Aligned. Score:  38
Sequences (2:8) Aligned. Score:  44
Sequences (2:9) Aligned. Score:  44
Sequences (2:10) Aligned. Score:  51
Sequences (2:11) Aligned. Score:  28
Sequences (2:12) Aligned. Score:  23
Sequences (2:13) Aligned. Score:  7
Sequences (3:4) Aligned. Score:  100
Sequences (3:5) Aligned. Score:  45
Sequences (3:6) Aligned. Score:  45
Sequences (3:7) Aligned. Score:  39
Sequences (3:8) Aligned. Score:  42
Sequences (3:9) Aligned. Score:  42
Sequences (3:10) Aligned. Score:  46
Sequences (3:11) Aligned. Score:  34
Sequences (3:12) Aligned. Score:  24
Sequences (3:13) Aligned. Score:  9
Sequences (4:5) Aligned. Score:  45
Sequences (4:6) Aligned. Score:  45
Sequences (4:7) Aligned. Score:  39
Sequences (4:8) Aligned. Score:  42
Sequences (4:9) Aligned. Score:  42
Sequences (4:10) Aligned. Score:  46
Sequences (4:11) Aligned. Score:  34
Sequences (4:12) Aligned. Score:  24
Sequences (4:13) Aligned. Score:  9
Sequences (5:6) Aligned. Score:  100
Sequences (5:7) Aligned. Score:  42
Sequences (5:8) Aligned. Score:  45
Sequences (5:9) Aligned. Score:  45
Sequences (5:10) Aligned. Score:  45
Sequences (5:11) Aligned. Score:  33
Sequences (5:12) Aligned. Score:  23
Sequences (5:13) Aligned. Score:  10
Sequences (6:7) Aligned. Score:  42
Sequences (6:8) Aligned. Score:  45
Sequences (6:9) Aligned. Score:  45
Sequences (6:10) Aligned. Score:  45
Sequences (6:11) Aligned. Score:  33
Sequences (6:12) Aligned. Score:  23
Sequences (6:13) Aligned. Score:  10
Sequences (7:8) Aligned. Score:  40
```

```
Sequences (7:9) Aligned. Score:  40
Sequences (7:10) Aligned. Score:  42
Sequences (7:11) Aligned. Score:  37
Sequences (7:12) Aligned. Score:  25
Sequences (7:13) Aligned. Score:  11
Sequences (8:9) Aligned. Score:  100
Sequences (8:10) Aligned. Score:  45
Sequences (8:11) Aligned. Score:  30
Sequences (8:12) Aligned. Score:  21
Sequences (8:13) Aligned. Score:  15
Sequences (9:10) Aligned. Score:  45
Sequences (9:11) Aligned. Score:  30
Sequences (9:12) Aligned. Score:  21
Sequences (9:13) Aligned. Score:  15
Sequences (10:11) Aligned. Score:  30
Sequences (10:12) Aligned. Score:  24
Sequences (10:13) Aligned. Score:  9
Sequences (11:12) Aligned. Score:  26
Sequences (11:13) Aligned. Score:  11
Sequences (12:13) Aligned. Score:  10
Guide tree        file created:   [baat5aiDp.dnd]
Start of Multiple Alignment
There are 12 groups
Aligning...
Group 1: Sequences:   2      Score:4208
Group 2: Sequences:   2      Score:4236
Group 3: Sequences:   3      Score:2159
Group 4: Sequences:   2      Score:4656
Group 5: Sequences:   5      Score:2034
Group 6: Sequences:   2      Score:4953
Group 7: Sequences:   7      Score:2036
Group 8: Sequences:   9      Score:2000
Group 9: Sequences:  10      Score:1865
Group 10:                    Delayed
Group 11:                    Delayed
Group 12:                    Delayed
Sequence:11     Score:1631
Sequence:12     Score:2065
Sequence:13     Score:1832
Alignment Score 43787
CLUSTAL-Alignment file created  [baat5aiDp.aln]
CLUSTAL W (1.7) multiple sequence alignment


g6715552              ------------------------------------------------------------
g13897995             ------------------------------------------------------------
g5919239              ------------------------------------------------------------
g10799394             ------------------------------------------------------------
SEQ_ID_NO_1           ------------------------------------------------------------
g6063386              ------------------------------------------------------------
g10799398             ------------------------------------------------------------
g4589283              ------------------------------------------------------------
g31075483             ------------------------------------------------------------
g1552516              ------------------------------------------------------------
TRY5_AEDAE/12-232     ------------------------------------------------------------
CTRL_HALRU/24-251     ------------------------------------------------------------
SP1_RARFA/205-391     MKCKKPSALFSALALVGALGAASVLGAASANSASPVAAATVQASSGSAKTSVAATSKSQD
```



```
g6715552              ------------------------------------------------------------
g13897995             ------------------------------------------------------------
g5919239              ------------------------------------------------------------
g10799394             ------------------------------------------------------------
SEQ_ID_NO_1           ------------------------------------------------------------
g6063386              ------------------------------------------------------------
g10799398             ------------------------------------------------------------
g4589283              ------------------------------------------------------------
g31075483             ------------------------------------------------------------
g1552516              ------------------------------------------------------------
TRY5_AEDAE/12-232     ------------------------------------------------------------
CTRL_HALRU/24-251     ------------------------------------------------------------
SP1_RARFA/205-391     GDVLAAIVRDLKITKTQAKKRIKLEEKARQLEPRLQKKLGKKPAGLWISKNGKKIVVGVT


g6715552              --------MFLLLTALQVLA---------IAMTQSQED----------------------
g13897995             --------MFLLLTALQVLA---------IAMTQSQED----------------------
g5919239              --------MKLGLLCALLSL---------LAGHGWAD-----------------------
g10799394             --------MKLGLLCALLSL---------LAGHGWAD-----------------------
SEQ_ID_NO_1           --------MWFLVLCLALS----------LGGTGAAPP----------------------
g6063386              --------MWPLALVIASLT---------LALSGGVSQESSKVL-----------------
g10799398             --------MWPLALVIASLT---------LALSGGVSQESSKVL-----------------
g4589283              --MATARPWMWVLCALITALLLGVTEHVLANNDVSCDHPSNTVPSGSNQDLGAGAGED-
g31075483             --MATARPWMWVLCALITALLLGVTEHVLANNDVSCDHPSNTVPSGSNQDLGAGAGED-
g1552516              --------MNPLLILAFVG----------AAVAVPFDD-----------------------
TRY5_AEDAE/12-232     ----------------------------TMVERSDS-----------------------
CTRL_HALRU/24-251     --------MNALLNILLCT----------LAATALAEI-----------------------
SP1_RARFA/205-391     TKKAAKVVKKAGATPKIVKSNLTTLKKRATKISKNAPSDIKNVNSWWVDPATNKVVIEAR


g6715552              ------ENKIIGGHTCTRSSQPWQAALLAGPRR----RFLCGGALLSGQW--VITAAHCG
g13897995             ------ENKIIGGHTCTRSSQPWQAALLAGPRR----RFLCGGALLSGQW--VITAAHCG
g5919239              -------TRAIGAEECRPNSQPWQAGLFHLT------RLFCGATLISDRW--LLTAAHCR
g10799394             -------TRAIGAEECRPNSQPWQAGLFHLT------RLFCGATLISDRW--LLTAAHCR
SEQ_ID_NO_1           -----IQSRIVGGWECEQHSQPWQAALYQKT------RLLCGATXXAPRW--FLTAAHCL
g6063386              -NTNGTSGFLPGGYTCFPHSQPWQAALLVQG------RLLCGGVLVHPKW--VLTAAHCL
g10799398             -NTNGTSGFLPGGYTCFPHSQPWQAALLVQG------RLLCGGVLVHPKW--VLTAAHCL
g4589283              ARSDDSSSRIINGSDCDMHTQPWQAALLLRPN-----QLYCGAVLVHPQW--LLTAAHCR
g31075483             ARSDDSSSRIINGSDCDMHTQPWQAALLLRPN-----QLYCGAVLVHPQW--LLTAAHCR
g1552516              ------DDKIVGGYTCEENSVPYQVSLNSGS-------HPCGGSLISEQW--VVSAGHCY
TRY5_AEDAE/12-232     ------SGRIVGGFEVPVEEVPFQVSLSGVGS-----SHPCGGSLLSERW--VMTAGHCA
CTRL_HALRU/24-251     ------SPNIVGGSNAAAGEPFWQGSLQVRSGTSW--FHICGCVLYTTSK--ALTAAHCL
SP1_RARFA/205-391     SKKAAKAAATAAGLTAGTYEITVSDDVIVPVRDYWGGDALSGCTLAFPVYGGFLTAGHCA
                                 .     . .  :          .*          ::*.**


g6715552              RP----ILQVALGKHNLR-RWEATQQVLRVVRQVTHPNYN------SRTHDNDLMLLQLQ
g13897995             RP----ILQVALGKHNLR-RWEATQQVLRVVRQVTHPNYN------SRTHDNDLMLLQLQ
g5919239              KP----YLWVRLGEHHLW-KWEGPEQLFRVTDFFPHPGFNKDLS--ANDHNDDIMLIRLP
g10799394             KP----YLWVRLGEHHLW-KWEGPEQLFRVTDFFPHPGFNKDLS--ANDHNDDIMLIRLP
SEQ_ID_NO_1           KP----RYIVHLGQHNLQ-KEEGCEQTRTATESFPHPGFNNSLP--NKDHRNDIMLVKMA
g6063386              KE----GLKVYLGKHALG-RVEAGEQVREVVHSIPHPEYRRSPT--HLNHDHDIMLLELQ
g10799398             KE----GLKVYLGKHALG-RVEAGEQVREVVHSIPHPEYRRSPT--HLNHDHDIMLLELQ
g4589283              KK----VFRVRLGHYSLSPVYESGQQMFQGVKSIPHPGYS------HPGHSNDLMLIKLN
g31075483             KK----VFRVRLGHYSLSPVYESGQQMFQGVKSIPHPGYS------HPGHSNDLMLIKLN
g1552516              KP----HIQVRLGEHNIE-VLEGNEQFINAAKIIRHPKYN------RITLNNDIMLIKLS
TRY5_AEDAE/12-232     ASGQ-TNLQVRIGSSQHA----SGGQLIKVKKVNRHPKYD------EVTTDYDFALLELE
CTRL_HALRU/24-251     SNSA-SSYRLGFGMLRMN-NVDGTEQYSSVTSYTNHPNYNGN----AAGYPNDIAVLRLT
SP1_RARFA/205-391     VEGKGHILKTEMTGGQIG-TVEAS-QFGDGIDAAWAKNYGDWNGRGRVTHWNGGGGVDIK
                            :         . *          :             .  : :
```

```
g6715552            --QPARIGRAVRPIEVTQA----------CASPGTSCRVSG-------WGTISSPIARY
g13897995           --QPARIGRAVRPIEVTQA----------CASPGTSCRVSG-------WGTISSPIARY
g5919239            --RQARLSPAVQPLNLSQT----------CVSPGMQCLISG-------WGAVSSPKALF
g10799394           --RQARLSPAVQPLNLSQT----------CVSPGMQCLISG-------WGAVSSPKALF
SEQ_ID_NO_1         --SPVSITWAVRPLTLSSR----------CVTAGTSCLISG-------WGSTSSPQLRL
g6063386            --SPVQLTGYIQTLPLSHN--N--------RLTPGTTCRVSG-------WGTTTSPQVNY
g10799398           --SPVQLTGYIQTLPLSHN--N--------RLTPGTTCRVSG-------WGTTTSPQVNY
g4589283            --RRIRPTKDVRPINVSSH----------CPSAGTKCLVSG-------WGTTKSPQVHF
g31075483           --RRIRPTKDVRPINVSSH----------CPSAGTKCLVSG-------WGTTKSPQVHF
g1552516            --TPAVINAHVSTISLPTA----------PPAAGTECLISG-------WGNTLSSGADY
TRY5_AEDAE/12-232   --ETVTFSDSCAPVKLPQKDT---------PVNEGTCLQVSG-------WGNTQNP-SES
CTRL_HALRU/24-251   --SSMDTSSSAVGPSVWLL--V--------ERLCRTNMYDQR-------MGKTQWR-WQH
SP1_RARFA/205-391   GSNEAAVGAHMCKSGRTTKWTCGYLLRKDVSVNYGNGHIVTLNETSACALGGDSGGAYVW
                                                                      *

g6715552            PASLQCVN-INISPDEVCQKAYP----------RTITPGMVCAGVPQGGKDSCQ----G
g13897995           PASLQCVN-INISPDEVCQKAYP----------RTITPGMVCAGVPQGGKDSCQ----G
g5919239            PVTLQCAN-ISILENKLCHWAYP----------GHISDSMLCAGLWEGGRGSCQ----G
g10799394           PVTLQCAN-ISILENKLCHWAYP----------GHISDSMLCAGLWEGGRGSCQ----G
SEQ_ID_NO_1         PHTLRCAN-ITIIEHQKCENAYP----------GNITDTMVCASVQEGGKDSCQ----G
g6063386            PKTLQCAN-IQLRSDEECRQVYP----------GKITDNMLCAGTKEGGKDSCE----G
g10799398           PKTLQCAN-IQLRSDEECRQVYP----------GKITDNMLCAGTKEGGKDSCE----G
g4589283            PKVLQCLN-ISVLSQKRCEDAYP----------RQIDDTMFCAGDKAG-RDSCQ----G
g31075483           PKVLQCLN-ISVLSQKRCEDAYP----------RQIDDTMFCAGDKAG-RDSCQ----G
g1552516            PDELQCLD-APVLTQAKCKASYP----------LKITSKMFCVGFLEGGKDSCQ----G
TRY5_AEDAE/12-232   SEVLRAAY-VPAVSQKECHKAYLSF---------GGVTDRMVCAGFKEGGKDSCQ----G
CTRL_HALRU/24-251   PNNLQKVD-MTVLTNSDCSSRWSGI---------SGATVNSGHICIFESGRSACS----G
SP1_RARFA/205-391   NDQAQGITSGSNMDTNNCRSFYQPVNTVLNKWKLSLVTSTDVTTSYVQGYQNNCIDVPNS
                       :          *   :                    . :. *     .

g6715552            DSG-GP----LVCRGQ-------------------LQGLVSWGM-------ERCALP---
g13897995           DSG-GP----LVCRGQ-------------------LQGLVSWGM-------ERCALP---
g5919239            DSG-GP----LVCNGT-------------------LAGVVSGGA-------EPCSRP---
g10799394           DSG-GP----LVCNGT-------------------LAGVVSGGA-------EPCSRP---
SEQ_ID_NO_1         DSG-GP----LVCNQS-------------------LQGIISWGQ-------DPCAIT---
g6063386            DSG-GP----LVCNRT-------------------LYGIVSWGD-------FPCGQP---
g10799398           DSG-GP----LVCNRT-------------------LYGIVSWGD-------FPCGQP---
g4589283            DSG-GP----VVCNGS-------------------LQGLVSWGD-------YPCARP---
g31075483           DSG-GP----VVCNGS-------------------LQGLVSWGD-------YPCARP---
g1552516            DSG-GP----VVCNGQ-------------------LQGIVSWG--------YGCAQK---
TRY5_AEDAE/12-232   DSG-GP----LVHDNT-------------------LVGVVSWG--------YGCAQA---
CTRL_HALRU/24-251   DSG-GP----LVCGNT-------------------LTGITSWGI-------SSCSG----
SP1_RARFA/205-391   DFTDGKQLQVWNCNGTNAQKVSFHPDGTLRINGKCLDARWAWTHNGTEVQLMNCNGHIAQ
                    *   *                              * .  :           *

g6715552            ----GYPGVYTNLCK-----YRSWIEETMRDK---------------
g13897995           ----GYPGVYTNLCK-----YRSWIEETMRDK---------------
g5919239            ----RRPAVYTSVCH-----YLDWIQEIMEN----------------
g10799394           ----RRPAVYTSVCH-----YLDWIQEIMEN----------------
SEQ_ID_NO_1         ----RKPGVYTKVCK-----YVDWIQETMKNN---------------
g6063386            ----DRPGVYTRVSR-----YVLWIRETIRKYETQQQKWLKGPQ---
g10799398           ----DRPGVYTRVSR-----YVLWIRETIRKYETQQQKWLKGPQ---
g4589283            ----NRPGVYTNLCK-----FTKWIQETIQANS--------------
g31075483           ----NRPGVYTNLCK-----FTKWIQETIQANS--------------
g1552516            ----RRPGVYTKVYN-----YVDWIKDTIAANS--------------
TRY5_AEDAE/12-232   ----GYPGVYARVAS-----VRDWVKEVSGL----------------
CTRL_HALRU/24-251   ----SYPSVYTRVSS-----FYNWVQTQ------------------
SP1_RARFA/205-391   KFTLNGAGDLVNVHANKCVDVKDWGGQGGKLQLWECSGGANQKWWRR
```


Submit sequences to: BLAST2 Submit Reset

IncyteGenomics